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Atty. Docket No. CRP-008DVFW  
(2054/6)

#28  
M.G.J.

BEFORE THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BOARD OF APPEALS

RECEIVED  
OCT 6 1994  
10/17/94

APPELLANTS: Huston et al.

SERIAL NO.: 08/014,096

GROUP NO.: 18121800

FILED: February 4, 1993

EXAMINER: Ulm, J.

TITLE: PRODUCE AND PROCESS FOR THE PRODUCTION, ISOLATION  
AND PURIFICATION OF RECOMBINANT POLYPEPTIDE

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Mailing Label No. TB576901743US, postage prepaid, in an envelope addressed to : The Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on September 20, 1994

Melanie Smith  
Melanie Smith

BRIEF ON APPEAL

The Honorable Commissioner of  
Patents & Trademarks  
Washington, D.C. 20231

Sir:

This is an appeal from the final rejection of claims 47-53, 56-61 and 63-68 as they were amended by Appellants' "Response Under 37 C.F.R. § 1.116" filed June 20, 1994. In an Advisory Action mailed from the Patent Office on July 5, 1994, the Examiner withdrew, in part, and affirmed, in part, the earlier rejections of the claims.

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I. STATUS OF THE CLAIMS

The claims on appeal are 47-53, 56-61 and 63-68. Claims 1-26 and 39-46 were cancelled during prosecution of the parent application U.S.S.N. 07/661,070, now abandoned. By an Amendment filed December 27, 1993, claims 27-38 were cancelled and claims 47-68 were added. Claims 47 and 64 were amended and claims 54, 55 and 62 were cancelled by the Amendment and Response After Final Rejection filed on June 20, 1994. As of July 5, 1994, claims 47-53, 56-61 and 63-68 remain pending in the instant application. The claims (as amended upon entry of an Appeal) appear in the Appendix attached hereto.

II. STATUS OF THE AMENDMENTS

In the final Office Action mailed from the Patent Office on March 30, 1994, claims 47-68 were rejected under 35 U.S.C. § 103; claims 54 and 55 were rejected under 35 U.S.C. § 112, fourth paragraph; and claim 62 was rejected under 35 U.S.C. § 112, first paragraph. Upon consideration of Appellants' Amendment After Final Rejection filed on June 20, 1994, the Examiner issued an Advisory Action indicating that rejection of claims 54, 55 and 62 under section 112 would be withdrawn upon filing of an Appeal. The Examiner also indicated that Appellants' proposed amendments to claims 47 and 64 filed on June 20, 1994 pursuant to 37 C.F.R. § 1.116 would be entered upon filing of an Appeal. Additionally, according to the above-referenced Advisory Action, the Examiner maintains rejection of amended claims 47-53, 56-61 and 63-68 under 35 U.S.C. § 103 as being unpatentably obvious over the Cousens et al. patent (1A, of record) in view of the Cohen et al. patent (1B, of record). A Notice of Appeal was filed on July 20, 1994.

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III. SUMMARY OF THE INVENTION

As defined by the newly amended claims, Appellants' invention relates to a fused polypeptide which comprises a combination of distinct, separate amino acid sequences. Said combination endows the overall fused polypeptide with intrinsic operativeness not associated with any one of its distinct component parts. This intrinsic operativeness is a direct consequence of the structural and conformational features imparted to the fused polypeptide by said combination. Appellants refer the Board to Figure 2 of their application for a pictorial representation of one of the combinations contemplated by Appellants' invention, and the structural and conformational features which directly result from said representative combination. Important to an appreciation of the instant invention's patentability is understanding that eventual recovery of that component of said fused polypeptide known as the selected target polypeptide is directly facilitated by the fused polypeptide's structural and conformational features. In essence, Appellants' invention is a combination of separate, distinct amino acid sequences which together endow the fused polypeptide with structural and conformational features critical to operativeness.

As defined by the amended claims, the instant invention is far more than a fusion polypeptide employing a selectively cleavable link at which an enzymatic cleavage agent acts to selectively cleave a precursor polypeptide. A critical point is that Appellants' cleavage site alone is not that feature of Appellants' invention which imparts operativeness. Rather, Appellants' combination of a distinct hinge region together with a cleavage site operates to permit ready release of said target polypeptide from the precursor polypeptide upon treatment with an enzymatic cleavage agent. This type of physico-chemical cooperation between said cleavage site and said hinge region of

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the instant invention is precisely articulated in the amended claims. The combination of a distinct hinge region with a particular cleavage site within the claimed fused polypeptide serves to present the fused polypeptide to the enzymatic cleavage agent such that preferential cleavage at the cleavage site occurs. Consequently, relative to prior art fusion proteins, recovery of intact, uncleaved target polypeptide is significantly facilitated.

#### IV. ISSUES

The issues presented for review are:

- (i) Whether the Cousens et al. patent U.S. 4,751,180 is properly entitled to the benefit of its abandoned predecessor's filing date, such that the Cousens et al. patent remains a prior art reference under section 102(e) for purposes of 35 U.S.C. § 103 in the instant application, in view of the holding in In re Wertheim, 646 F.2d 527 (C.C.P.A. 1981); and,
- (ii) Whether amended claims 47-53, 56-61, and 63-68 are patentably unobvious under 35 U.S.C. § 103 over the Cousens et al. patent in view of the prior art reference U.S. 4,743,679 issued to Cohen et al.

#### V. GROUPING OF CLAIMS

Appellants request that the claims be grouped for consideration by the Board as follows:

Group I: claims 47-53, 56-61, and 63  
Group II: claims 64-68

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Appellants believe that the ground of rejection under 35 U.S.C. § 103 applies separately to more than just the single group of claims designated by the Examiner. Additionally, Appellants consider the rejected claims to be separately patentable. Group I is drawn to a fused polypeptide produced by an organism by expression of a recombinant DNA comprising a combination of amino acid sequences. Group II is drawn to a fused polypeptide encoded by a recombinant DNA comprising a combination of DNA segments.

Pursuant to the requirement of 37 C.F.R. 1.192(c)(5), Appellants hereby assert that the claims do not stand or fall together, and that the claim groups set forth above represent separately patentable subject matter. As required by 37 C.F.R. 1.192(c)(6), the reasons why Appellants consider the claims separately patentable are set forth below in the appropriate parts of "Appellants' Arguments." Appellants submit that inclusion below of such reasons obviates any concerns that Appellants' assertions of separate patentability are unsupported.

VI. APPELLANTS' ARGUMENTS

Rejection of amended claims 47-53, 56-61 and 63-68 under  
35 U.S.C. § 103

In the above-referenced Advisory Action, the Examiner stated that amended claims 47-53, 56-61 and 63-68 remained rejected under 35 U.S.C. § 103 as being unpatentable over the Cousens et al. continuation-in-part patent U.S. 4,751,180 (1A of record) in view of the Cohen et al. patent U.S. 4,743,679 (1B of record) essentially for those reasons of record set forth in Paper Number 24.

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As indicated above, Appellants consider the ground of this rejection to be applicable separately to each of claim Groups I and II. Group I is drawn to a fused polypeptide produced by an organism by expression of a recombinant DNA comprising a combination of amino acid sequences. As discussed below, Appellants submit that the claims of Group I are patentably unobvious over the prior art cited.

Group II is drawn to a fused polypeptide produced by an organism by expression of a recombinant DNA and encoded by a recombinant DNA comprising a combination of DNA segments. As will be discussed below, the claims of Group II are also patentably unobvious over the prior art cited.

Pursuant to 37 C.F.R. § 1.192 (c)(6)(iv), the following argument discusses the legal standard applicable to the instant application, specifies the errors in the rejections, and the specific limitations in the rejected claims which are not described in the prior art relied on in the rejection, and explains how such limitations render the claimed subject matter unobvious over the prior art. Moreover, since the instant rejection is based upon a combination of references, the following argument explains why the references, taken as a whole, do not suggest the claimed subject matter, and why features disclosed in the primary reference (Cousens et al.) are not properly combinable with features disclosed in the secondary reference (Cohen et al.).

#### Procedural Background of the Instant Application

Before presenting the substance of their legal argument, Appellants wish to review the pertinent prosecution events in the instant case. During prosecution of the instant application,

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Appellants swore behind the March 28, 1986 filing date of the Cousens et al. continuation-in-part patent U.S. 4,751,180 [hereinafter referred to as the subsequent '180 patent] which derived from an abandoned patent application U.S.S.N. 07/717,209 by Cousens et al. [hereinafter referred to as the remote or abandoned '209 predecessor application]. By so doing, Appellants successfully eliminated the continuation-in-part patent as a prior art reference. But, by applying a relation-back principle purportedly pursuant to 35 U.S.C. § 120, the Examiner ruled that the Cousens et al. subsequent '180 patent would remain in the instant case as prior art under section 102(e) for section 103 purposes because its abandoned predecessor, the '209 patent application, antedated Appellants' declaration. In essence, the inventors of the patentable subject matter in the subsequent '180 patent were afforded the exclusionary benefit of the abandoned predecessor application's earlier filing date under the auspices of section 120.

The applicable law: In re Wertheim (C.C.P.A. 1981)

As a threshold matter, Appellants take exception with the Examiner's characterization of the Cousens et al. abandoned '209 application as a prior art reference under section 102(e) for the purposes of section 103. Appellants firmly believe that the Examiner's use of the Cousens et al. '209 abandoned application is contrary to In re Wertheim, 646 F.2d 527 (C.C.P.A. 1981).

The limited circumstances under which the relation-back principle of section 120 may be applied are carefully described in In re Wertheim. In Wertheim the court addressed the issue of when a patent is entitled to the benefit of the filing date of a remote application. The Wertheim court framed the specific issue as follows: "What patent disclosure, or portion thereof, which



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has been "carried over" through a chain of applications, may be traced back to an earlier application and given its effective date, and then combined with a secondary reference to reject later filed claims under §§ 102(e)/103?"

Specifically, the court stated that "an abandoned application by itself can never be a reference." Id. at 535. According to Wertheim, the critical legal issue is whether the invention claimed in the subsequent patent finds a supporting disclosure in compliance with section 112, as required by section 120, in the abandoned application so as to entitle that invention to the filing date of the abandoned application for prior art purposes. Id. at 537. If the disclosures of the remote application do not fully support a claim in the patent, or if the claims of the subsequent patent derive essential support from new matter added by later continuation-in-part applications, then it is not effective for prior art purposes under section 102(e) and 103 as of the remote filing date. This is true even though the disclosed matter in question appeared in the remote application and is carried forward into the patent. In this regard, the Wertheim court stated:

We emphasize that the above noted statutes, §§ 102(e), 120, and 112, speak with reference to some specific claimed subject matter . . . . It is axiomatic in patent law that questions of description, disclosure, enablement, anticipation, and obviousness can only be discussed with reference to a specific claim which identifies "the invention" referred to in the statutes.

Thus, the determinative question here is whether the invention claimed in the [subsequently issued patent] finds a supporting disclosure in compliance with § 112, as required by § 120, in the [remote application] so as to entitle that invention in the [subsequent patent], as "prior art," to the filing date of [the remote application]. Without such support, the invention, and its accompanying disclosure, cannot be regarded as prior art as of that filing date.

Id. at 537 (emphasis added).

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Furthermore, Wertheim criticized and accordingly modified two earlier cases which relied merely on the fact that disclosures in remote or abandoned applications had been "carried over" to later applications. The two modified cases are In re Switzer, 166 F.2d (C.C.P.A. 1948) and In re Lund, 376 F.2d 982 (C.C.P.A. 1967).

Like the Examiner in Wertheim, and as admitted by the Examiner in the instant case in Paper Number 16, page 2 line 16 through page 3 line 9, the Examiner in the instant application has abstracted that portion of the disclosure in the '209 predecessor application which is "common to both" the predecessor and its subsequent '180 continuation-in-part patent, i.e., that portion which is "carried over" into the subsequent patent, and effectively used it in combination with a second reference to reject the instant claims as obvious. In this regard, the Wertheim court said "[f]or the reasons which follow, we hold that was erroneous." In re Wertheim at 535. Relying on the Wertheim rationale, Appellants submit that the instant Examiner's use of the Cousens et al. '209 predecessor application (and its filing date) is similarly erroneous.

Application of the legal standard of In re Wertheim to the instant case

Wertheim is particularly relevant to the instant case in that it, too, involves an abandoned patent application and the continuation-in-part patent derived therefrom. As pointed out by Wertheim, new matter can add material limitations which transform an unpatentable invention into a patentable one. A continuation-in-part application does not necessarily insure that all critical aspects of the subsequent application were present in the remote predecessor application. Thus, in such a situation, only a remote application disclosing the patented invention as required

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by section 112 before the addition of new matter can be relied upon to give the subsequent patent the benefit of the earlier filing date for the purpose of supporting a section 102(e)/103 rejection.

As was also true in Wertheim, instead of determining what filing date the subsequent '180 patent was entitled to as a § 102(e) reference for purposes of the §§ 102(e)/103 rejection, the instant Examiner relied upon the erroneous rationale that a disclosure which is "carried over" into the patent from previous applications may be used to defeat the patent rights of another inventor. In other words, rather than examining the subsequent '180 patent in light of §§ 120 and 112, the Examiner reached back to the abandoned '209 predecessor application and retrieved that portion "carried over" into the patent and combined it with a secondary reference to find the instant invention obvious. In re Wertheim at 536.

If an Examiner "wishes to utilize against an applicant a part of that patent disclosure found in an application filed earlier than the date of the application which became the patent," the Examiner

must demonstrate that the earlier-filed application contains §§ 120/112 support for the invention claimed in the reference patent. For if a patent could not theoretically have issued the day the application was filed, it is not entitled to be used against another . .

. .

. . .

Thus, in a situation such as this, only an application disclosing the patentable invention before the addition of new matter, which disclosure is carried over into the patent, can be relied upon to give a reference disclosure the benefit of its filing date for the purpose of supporting a §§ 102(e)/103 rejection.

In re Wertheim at 537.

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The only date the Cousens et al. subsequent '180 patent has under § 102(e) is March 28, 1986, the filing date of the application on which the '180 patent issued. Any earlier U.S. filing date for the patent necessarily depends on further compliance with §§ 120 and 112. The Examiner appears to have assumed the existence of the very point at issue here--whether the Cousens et al. '180 patent is entitled to an earlier filing date of March 28, 1985.

Comparison of the claims of the subsequent '180 continuation-in-part patent with the disclosure of the '209 abandoned predecessor application

Keeping in mind the above-described legal standard, Appellants will now discuss in detail the critical differences between these two disclosures.

As was true in Wertheim, there are at least two claim limitations missing from the '209 predecessor application but present in the '180 subsequent patent "which answer the question of whether to award the [earlier] filing date to the § 102(e) reference patent disclosure." "If either limitation, later added as new matter, resulted in the disclosure of a patentable invention for the first time, it is relevant to determination of whether [the '180 patent] receives the benefit of the ['209 predecessor application] filing date." In re Wertheim at 538. In this regard, the '209 predecessor application did not "expressly disclose" either "hinge amino acids" or "hinge sequences."

For example, Appellants refer the Board to issued claims 16, 19, and 20-22 in the subsequent '180 patent. These are the issued claims which define the patentee's "hinge amino acids" and

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fusion proteins containing such amino acids. Appellants submit that absent from the '209 predecessor application is any supporting specification for such claims.

For the Board's convenience and information, Appellants have included a copy of the pertinent issued claims from the '180 patent (see Exhibit A attached hereto), as well as a copy of the pertinent portions of the disclosure of the '209 predecessor application (see Exhibit B attached hereto). Upon a comparison of the issued claims with the abandoned application's disclosure, Appellants submit that the "hinge amino acids" of claim 16, and "hinge sequence" of claims 19, 20, 21, and 22 simply do not find a supporting disclosure in compliance with section 112 in the '209 predecessor application. Appellants also submit that the "cleavable link" defined as an "enzymatically removable link" in claim 17 also lack support under section 112. Appellants' rationale is as follows.

With respect to "hinge amino acids" in claim 16 of the subsequent '180 patent, the '209 predecessor application does not contain that term, does not define that term, does not teach the artisan how to make or use, and does not set forth the best mode contemplated. As such, the subject matter of claim 16 is not properly enabled under section 112. Keeping in mind the above-described legal standard set forth in Wertheim, the invention of claim 16 is not properly entitled to the filing date of the predecessor application and thus, can not antedate Appellants' invention.

Similarly, the "hinge sequence" recited by claims 19, 20, 21, and 22 is a term which does not appear in the '209 predecessor patent and is not defined therein. Moreover, the '209 predecessor application does not teach the artisan how to make or

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use, and does not set forth the best mode contemplated as required by section 112. Again, the invention of claims 19, 20, 21, and 22 are not properly entitled to the filing date of the predecessor application and thus, do not antedate Appellants' invention.

With respect to claim 17, the '209 predecessor application does not teach the artisan how to use "enzymatically removable" links. The only disclosed species of fusion protein cleaved was a protein containing a methionine cleavable link, removable by chemical cleavage with cyanogen bromide.

As was also true in Wertheim, the Examiner in the instant case does not attach any significance to the absence of express language disclosing "hinge amino acids" or "hinge sequences." Since the '209 predecessor application merely listed, but neither discussed nor described, two amino acid sequences in Table 1 on page 15, the Examiner determined that the above concept was inherently disclosed in the '209 predecessor application. See id. at 538. Moreover, the Examiner gives little weight to the addition of completely dissimilar "hinge" sequences in the subsequent '180 continuation-in-part patent. Thus, the Examiner apparently does not find any of the above claim limitations to be new matter, much less relevant new matter.

To further support these conclusions, Appellants have also included a copy of those portions of the subsequent '180 patent which are unequivocally "new matter" relative to its predecessor (see Exhibit C attached hereto). [For the Board's convenience, Appellants have specifically indicated (by hi-lighting in yellow) the text absent from the '209 predecessor application but present in the subsequent '180 patent.] As discussed below, it is readily obvious that the above limitations relating to patentee's "hinge amino acids" were relevant, indeed, critical new matter.

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For example, Appellants request that the Board compare both the Table on page 15 and the specification on page 5 of the abandoned '209 application, with column 4 and Table 1 of the subsequent '180 continuation-in-part patent. Specifically, at column 4, lines 16-48, the '180 patent recites the following new matter:

In addition to the amino acids comprising the cleavable site, it may be advantageous to separate further the two fused polypeptides. Such a "hinge" would allow for steric flexibility so that the fused polypeptides would be less likely to interfere with each other, thus preventing incorrect folding, blockage of the cleavage site, or the like.

The "hinge" amino acid sequence could be of variable length and may contain any amino acid side chains so long as the side chains do not interfere with the mode of action employed to break at the cleavable site . . . . Preferably the amino acids comprising the hinge would have side chains that are neutral and either polar or nonpolar and may include one or more prolines. The hinge region will have at least one amino acid . . . .

. . . .  
So that the "hinge" amino acids are not bound to the final cleaved polypeptide of interest, it is desirable, but not required to practice the invention, to place the "hinge" between the polypeptide that is produced independently at high yield and the sequence for the cleavable site. (Emphasis added)

Corresponding to this new matter are numerous new experimental entries in Table 1 of the subsequent '180 patent (Table 1 appears at column 10). In fact, these new entries are specifically labeled as "hinge" and are distinguishable from the original entries which do not illustrate SOD-Met-Proinsulin fusion proteins containing a "hinge" as that term is used in the subsequent '180 patent. Additionally, the data in Table 1 summarize the experiments of Examples II through III which appear at columns 12 to 17 of the subsequent '180 continuation-in-part patent, but are absent from the '209 abandoned application.

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Clearly, in view of this evidence, the Board can not reasonably affirm the Examiner's continued assertion that the subsequent '180 continuation-in-part patent derives the benefit of its abandoned predecessor's earlier filing date. Appellants submit that, upon reading the subsequent '180 patent, it is clear that the above-referenced claim recitations and corresponding new matter are a necessary part of the patentable invention set forth in the subsequent '180 continuation-in-part patent. These limitations and new matter, however, are neither expressly nor inherently part of the '209 predecessor application. Thus, absent these limitations and new matter, reliance on the earlier filing date and effective use of the '209 predecessor application to transform the '180 subsequent patent into prior art is not legally permissible and in direct contravention of the holding in Wertheim.

In short, the Examiner erred in determining that, since the substance of the relevant disclosure in the '209 predecessor application was carried forward into the subsequent '180 continuation-in-part patent, that same disclosure in the '180 patent was entitled to the earlier '209 filing date, even though the entire of the '180 patent was not. "While some of the reference patent disclosure can be traced to [the '209 predecessor application], such portions of the original disclosure cannot be found "carried over" for the purpose of awarding filing dates, unless that disclosure constituted a full, clear, concise and exact description in accordance with § 112, first paragraph, of the invention claimed in the [subsequent '180 continuation-in-part] patent, else the application could not have matured into a patent, within the Milburn § 102(e) rationale, to be prior art under § 103." In re Wertheim at 538-539.

Without the benefit of the earlier date, Appellants'



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previously-submitted Declaration is sufficient to eliminate consideration of the Cousens et al. '180 patent reference, in whole or in part, as prior art to be combined with another reference to support a section 103 rejection. Recall that the Examiner has rejected amended claims 47-53, 56-61 and 63-68 under 35 U.S.C. § 103 as being unpatentable over the Cousens et al. patent combined with the Cohen et al. patent. In view of the holding in In re Wertheim, however, the Cousens et al. '180 patent must be removed as a prior art reference in the instant case.

The Examiner in the instant application, as did the Examiner in Wertheim, has improperly maintained the final rejection of Appellants' claims under 35 U.S.C. § 103 in view of a combination of two references, one of which having been erroneously accorded the benefit of an earlier filing date. According to Wertheim, the Cousens et al. '180 patent disclosure used in the present rejection is not effective as a reference as of the filing date of its abandoned '209 predecessor application. Thus, the '180 patent does not antedate Appellants' declared reduction to practice and thus can not be combined with another reference to support a rejection for obviousness under section 103. In re Wertheim at 539. Again, Wertheim clearly stands for the proposition that the "[predecessor] application, the filing date of which is needed to make a rejection, must disclose, pursuant to §§ 120/112, the invention claimed in the [subsequent continuation-in-part] reference patent." Id.

Even if, however, the Board should determine that the "carried over" portion of the Cousens et al. '180 patent is prior art under section 102(e) for purposes of section 103, Appellants submit that the instant invention is still patentable over that portion of the Cousens et al. '180 patent in view of the Cohen et

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al. patent for the following reasons. The Examiner's section 103 rejection is discussed below in the context of the amended claims.

As defined by the amended claims, the instant invention is far more than a fusion polypeptide employing "a selectively cleavable link," at which an enzymatic cleavage agent acts to selectively cleave a precursor polypeptide. A critical distinction between the earlier Cousens et al. disclosure and Appellants' invention is that Appellants' cleavage site alone is not that feature of Appellants' invention which imparts operativeness. Rather, Appellants' combination of a distinct hinge region together with a cleavage site operates to permit ready release of said target polypeptide from the precursor polypeptide upon treatment with an enzymatic cleavage agent. This type of physico-chemical cooperation between said cleavage site and said hinge region achieved by the instant invention is precisely articulated in the amended claims. No such teaching or suggestion of an operative combination of a distinct cleavage site and a distinct hinge region appears in the earlier Cousens et al. disclosure. The combination of a distinct hinge region with a particular cleavage site within the claimed fused polypeptide serves to present the fused polypeptide to the enzymatic cleavage agent such that preferential cleavage at the cleavage site occurs. Consequently, recovery of intact, uncleaved target polypeptide is significantly facilitated. No such teaching or suggestion concerning operativeness can be found in the Cousens et al. This feature of Appellants' claimed combination further supports the conclusion that their invention is patentably unobvious over Cousens et al.

The final Office Action further asserts that the '209 predecessor application implicitly teaches a hinge-like flexible structure which promotes cleavage. Similarly, it further states that artisans like Cousens et al. would have appreciated use of a

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flexible linker without explicitly stating so. Appellants respectfully point out that it is a well-settled legal principal that in order for a rejection to be based upon a property that is inherent in the prior art, such inherency must be necessary and certain. In Interchemical Corp. v. Watson, 145 F. Supp. 179, 182 (D.D.C. 1956), aff'd 251 F.2d 390 (D.C. Cir. 1958), the court stated that "[t]he law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable."

Given the subject matter of the Cousens et al. '209 disclosure, the necessary and certain legal standard can not be met. There is no basis for properly concluding that a flexible, hinge-like structure with the operativeness claimed by Appellants is a necessary and certain consequence of the Cousens et al. disclosure. The references supplied by the Examiner (Lehninger and Lofdahl) do not, in the opinion of Appellants, speak to this issue. Furthermore, as stated above, Cousens et al. failed to even recognize the problem solved by Appellants, and contained no teaching or suggestion of the claimed combination of elements or the unexpected results obtained in using it.

The proper standard for a rejection under section 103 is set out in Graham v. John Deere Co., 148 U.S.P.Q. 459 (S.Ct. 1966). In order for an obviousness rejection under section 103 to be proper, the Examiner must show that the essential elements defined by the Appellants' claims as they relate to the "subject matter as a whole" are taught or suggested by the cited art. In the case of the instant invention, it is Appellants' claimed combination which is inventive. Appellants' amended claims relate to a combination of distinct and separate amino acid sequences which endow the overall fused polypeptide with certain conformational and structural features operable to facilitate

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selective recovery of a target polypeptide. Such a combination is neither taught nor suggested by the prior art.

Under the proper standard for obviousness, every attempt at showing a prima facie case of obviousness must show cognizance of all of the differences between the claimed subject matter and the prior art, as well as for the effect those differences create. Id. at 467. The differences between Appellants' claimed subject matter and both of the Cousens references were exhaustively discussed above. These differences would not have been obvious to one skilled in the art because the cited references do not teach, suggest, or motivate one to practice Appellants' claimed combination invention.

Cohen et al. U.S. 4,743,679 [hereinafter referred to as '679] teaches that the elimination of cysteine residues in a leader-type peptide prevents possible interactions and interferences with the obligatory formation of disulfide bridges. The Examiner suggests that this teaching, in view of the earlier Cousens et al. disclosure, renders Appellants' claimed combination unpatentably obvious. Appellants believe that the Examiner's rejection is predicated upon an improper combination of the earlier Cousens et al. disclosure with the Cohen et al. '679 reference. The law of combination of references is clearly stated in Eversharp, Inc. v. Fisher Pen Co., Inc., 132 U.S.P.Q. 423 (N.D.Ill. 1961):

In order for one to defeat a meritorious patent it is not enough to pick out isolated features in earlier prior art patents, combine them in one particular way with hindsight acquired only from the patent under attack, and then say that no invention would have been involved in selecting those particular features and combining them in the particular way in which the patentee did.

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In fact, in citing this Eversharp case, the district court in Matherson-Selig Co. v. Color Card, Inc., 154 U.S.P.Q. 265 (N.D.Ill. 1967) stated:

References may be combined to establish obviousness, but they must suggest the combination itself and not merely all of the elements which make up the combination, for it is the combination and not the individual elements that comprise the invention.

The claimed combination is unique and achieves results that would not have been obvious to a skilled artisan relying solely upon Cousens et al. with or without Cohen et al., since neither reference recognized the problem solved by Appellants. One skilled in the art relying upon these reference would not have been motivated to combine them because the Cousens et al. and Cohen et al. references, taken singly or combined, do not teach or suggest the combination of separate and distinct amino acid sequences which comprise the Appellants' claimed subject matter as a whole, nor the advantages obtained thereby. Furthermore, neither Cousens et al. or Cohen et al. provides the required teaching, suggestions, or incentive which would have led one of ordinary skill in the art to combine the relevant teachings of the references.

## VII. CONCLUSION

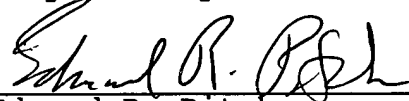
For the reasons set forth above, Appellants believe that the Cousens et al. subsequent '180 patent has been improperly afforded the benefit of its abandoned predecessor's earlier filing date. Accordingly, the Cousens et al. '180 patent does not antedate Appellants previously submitted Declaration and is thus not prior art under section 102(e) for purposes of

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section 103. Furthermore, Appellants believe that the pending claims as amended are patentably unobvious over the cited combination of prior art references under section 103. Accordingly, Appellants respectfully request reversal of the rejection of claims 47-53, 56-61, and 63-68 in the instant application.

Respectfully submitted,

  
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#### APPENDIX

47. A fused polypeptide produced by an organism by expression of a recombinant DNA, said polypeptide comprising a combination of:

a first sequence of amino acids comprising a leader sequence, a hinge region, and at least one amino acid defining a cleavage site recognizable and cleavable by a selected enzymatic cleavage agent,

said hinge region being a cysteine-free flexible amino acid sequence not normally associated with said leader sequence and comprising at least two amino acids defining a secondary structure which promote cleavage by said cleavage agent at said cleavage site, and

a second sequence of amino acids linked to said first sequence defining a selected target polypeptide, whereby said cleavage site is a favored site for cleavage upon treatment of said fused polypeptide with said cleavage agent when said fused polypeptide is disposed in solution and said second amino acid sequence defining said selected target polypeptide is disposed in its three-dimensional conformation.

48. The fused polypeptide of claim 47 wherein said leader sequence is adapted to facilitate concentration of said fused polypeptide.

49. The fused polypeptide of claim 48 wherein said leader sequence comprises an amphiphilic helix.

50. The fused polypeptide of claim 47 wherein said hinge region comprises at least one proline residue.

51. The fused polypeptide of claim 47 wherein said hinge region comprises an amino acid sequence which forms a random coil when said fused polypeptide is disposed in aqueous solution.

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52. The fused polypeptide of claim 47 wherein said hinge region includes a member selected from the group consisting of aspartic acid, glutamic acid, lysine, arginine, serine, threonine, proline, and combinations thereof in amounts sufficient to render said hinge region soluble in water

53. The fused polypeptide of claim 47 wherein said hinge region comprises:

a flexible cysteine-free amino acid sequence not normally associated with said leader sequence or said selected target polypeptide.

56. The fused polypeptide of claim 47 wherein said cleavage site is rendered preferentially accessible to said cleavage agent by said hinge region, thereby promoting preferential cleavage of said target polypeptide from said first sequence at said cleavage site in an environment in which said target polypeptide is disposed in its three dimensional conformation.

57. The fused polypeptide of claim 47 wherein said cleavage site is immediately adjacent said second amino acid sequence.

58. The fused polypeptide of claim 47 wherein said cleavage site comprises one or a sequence of amino acids absent from the sequence comprising said target polypeptide.

59. The fused polypeptide of claim 47 wherein said cleavage site comprises a unique one or sequence of amino acids in said fused polypeptide.

60. The fused polypeptide of claim 47 wherein said cleavage site comprises a Glu residue.

61. The fused polypeptide of claim 60 wherein said cleavage site is cleaved by *S. aureus* V-8 protease.



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63. The fused polypeptide of claim 47 wherein said target polypeptide is selected from the group consisting of growth factors, hormones, lymphokines, enzymes, antibody binding sites, viral proteins, non-enzymatically active prokaryotic proteins, and analogs thereof.

64. A fused polypeptide produced by an organism by expression of a recombinant DNA, said fused polypeptide encoded by a recombinant DNA comprising a combination of:

- a first DNA segment encoding a sequence of amino acids comprising a leader sequence, a hinge region, and at least one amino acid defining a cleavage site recognizable and cleavable by a selected enzymatic agent,

- said hinge region being a cysteine-free flexible amino acid sequence not normally associated with said leader sequence and comprising at least two amino acids defining a secondary structure which can promote cleavage by said cleavage agent at said cleavage site; and

- a second DNA segment linked to said first segment encoding a sequence of amino acids defining a selected target polypeptide, whereby said cleavage site is a favored site for cleavage upon treatment of said fused polypeptide with said cleavage agent when said fused polypeptide is disposed in solution and said amino acid sequence defining a target polypeptide is disposed in its three dimensional conformation.

65. The fused polypeptide of claim 64 wherein the recombinant DNA encoding said first DNA segment comprises

- DNA encoding a leader sequence comprising an amino acid sequence which imparts a preselected property to said fused polypeptide operable to facilitate concentration of said fused polypeptide.

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66. The fused polypeptide of claim 64 wherein the recombinant DNA encoding said cleavage site comprises

DNA encoding one or a sequence of amino acids absent from said sequence defining said target polypeptide.

67. The fused polypeptide of claim 64 wherein the recombinant DNA encoding said hinge region comprises

DNA encoding a flexible cysteine-free amino acid sequence not normally associated with said leader sequence or said selected target polypeptide.

68. The fused polypeptide of claim 64 wherein the recombinant DNA encoding said second segment comprises

a sequence of amino acids defining growth factors, hormones, lymphokines, enzymes, antibody binding sites, viral proteins, non-enzymatically active procaryotic proteins, and analogs thereof.